



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Cobicistat (COBI, Tybost) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Tablet: 150 mg

Fixed-Dose Combination Tablets:

- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Prezcobix] Darunavir 800 mg/cobicistat 150 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir alafenamide 10 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

Dosing Recommendations

Cobicistat is a Pharmacokinetic Enhancer:

- The only use of cobicistat (COBI) is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase strand transfer inhibitors. COBI **is not interchangeable** with ritonavir (RTV).

Child and Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- COBI 150 mg with atazanavir (ATV) 300 mg administered at the same time and with food

Child and Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- COBI 150 mg with darunavir (DRV) 800 mg administered at the same time and with food

[Evotaz] Atazanavir/Cobicistat

Child and Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- One tablet once daily with food
- Use in combination with other ARV drugs.

[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)

Child and Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- One tablet once daily with food

[Prezcobix] Darunavir/Cobicistat

Child and Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- One tablet once daily with food

Selected Adverse Events

- COBI is an inhibitor of renal tubular transporters of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate, with no change in glomerular function.

Special Instructions

- COBI 150 mg **is not interchangeable** with RTV, but it has a PK boosting effect that is comparable to RTV 100 mg.
- Drug interactions may differ between RTV and COBI, because COBI is a stronger P-glycoprotein inhibitor and lacks some of the induction effects of RTV.
- **Do not administer** COBI with RTV or with FDC tablets that contain COBI.
- COBI **is not recommended** for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir used in combination with a PI).
- Using COBI with PIs other than once-daily ATV 300 mg or DRV 800 mg **is not recommended**.
- Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline should be closely monitored for renal safety.
- When using COBI in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while the patient is receiving therapy (see [Table 15i](#)). In patients who are at risk of

- Use in combination with other ARV drugs.

[Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- One tablet once daily with food
- The Panel recommends using Stribild only in patients with sexual maturity ratings of 4 or 5.

[Symtuza] Darunavir/Cobicistat/Emtricitabine/TAF
Child and Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- One tablet once daily with food

renal impairment, serum phosphate should also be monitored.

- For information on crushing and cutting tablets, please see [this table](#) from Toronto General Hospital.

Metabolism/Elimination

- COBI is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6.

Cobicistat Dosing in Patients with Hepatic Impairment:

- COBI does not require dose adjustment in patients with mild to moderate hepatic impairment. No data are available in patients with severe hepatic impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.¹
- Stribild, Genvoya, and Symtuza **should not be used** in patients with severe hepatic impairment.¹

Cobicistat Dosing in Patients with Renal Impairment:

- COBI does not require a dose adjustment in patients with renal impairment, including those with severe renal impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.¹
- The use of COBI plus TDF **is not recommended** in patients with creatinine clearance (CrCl) <70 mL/min. Dose adjustments for TDF are required for patients with CrCl <50 mL/min, and the necessary dose adjustments for TDF when this drug is used with COBI have not been established in this group of patients.¹
- Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min. The dose adjustments required for emtricitabine and TDF in these patients cannot be achieved with an FDC tablet.
- Neither Genvoya nor Symtuza should be initiated in patients with estimated CrCl <30 mL/min.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and [HIV Drug Interaction Checker](#))

- **Metabolism:** Metabolism of cobicistat (COBI) is mainly via cytochrome P450 (CYP) 3A4 and, to a lesser degree, CYP2D6. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. COBI

also inhibits the breast cancer resistance protein, P-glycoprotein (P-gp), the organic anion transporting polypeptides OATP1B1 and OATP1B3, and multidrug and toxin extrusion 1 (MATE1). Unlike ritonavir (RTV), COBI does not demonstrate any enzyme-inducing effects. The potential exists for multiple drug interactions when using COBI. Before COBI is administered, a patient's medication profile should be carefully reviewed for potential interactions and overlapping toxicities with other drugs.

- *Nucleoside reverse transcriptase inhibitors:* COBI is a strong P-gp inhibitor; thus, a dose of tenofovir alafenamide (TAF) 10 mg combined with COBI produces tenofovir (TFV) exposures that are similar to those produced by TAF 25 mg without COBI.² **COBI increases plasma TFV exposures by 23% when it is coadministered with TDF; thus, renal safety should be monitored in patients who are receiving this combination.**^{1,3}
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine **should not be used** with COBI.
- *Protease inhibitors:* Using COBI as a dual booster for elvitegravir (EVG) and darunavir (DRV) has been studied in people with HIV and people without HIV, and the evidence is conflicting. When EVG plus COBI plus DRV was administered to people without HIV, the C_{trough} concentration of EVG was 50% lower than the C_{trough} concentration seen in people who received elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) without DRV.⁴ When EVG/c/FTC/TAF was administered with DRV to patients with HIV, both DRV and EVG concentrations were comparable to those seen in historic controls.⁵
- *Integrase inhibitors:* In one small study, dolutegravir (DTG) C_{trough} concentrations were 107% higher when DTG was administered with darunavir/cobicistat (DRV/c) than when it was administered with darunavir/ritonavir.⁶ Bictegravir (BIC) area under the curve increases 74% when BIC is administered with DRV/c.⁷
- *Corticosteroids:* Increased serum concentrations of corticosteroids can occur when corticosteroids and COBI are coadministered; this can lead to clinically significant adrenal suppression. Adrenal suppression occurs regardless of whether the corticosteroids are administered orally or by some other route (e.g., intranasal, inhaled, interlaminar, intraarticular) and regardless of whether the corticosteroids are administered routinely or intermittently. A possible exception is beclomethasone, which appears to be a relatively safe option with inhaled or intranasal administration.^{8,9}

Major Toxicities

- *More common:* Nausea, vomiting, diarrhea, abdominal pain, anorexia.
- *Less common (more severe):* New onset renal impairment or worsening of renal impairment when used with TDF. Rhabdomyolysis; increased amylase and lipase levels.

Resistance

Not applicable. COBI has no antiviral activity. Its sole use is as a pharmacokinetic enhancer of antiretroviral drugs.

Pediatric Use

Approval

COBI, as a component of Stribild, is approved by the Food and Drug Administration (FDA) at the adult dose for use in children and adolescents aged ≥ 12 years and weighing ≥ 35 kg. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends limiting the use of Stribild to those with a sexual maturity rating of 4 or 5. COBI, as a component of Genvoya, is approved by the FDA at the adult dose for use in children weighing ≥ 25 kg. **COBI alone (as Tybost) is approved by the FDA at the adult dose for use in children weighing ≥ 35 kg when used in combination with ATV, and in children weighing ≥ 40 kg when used in combination with DRV.** The FDA has not approved the use of COBI

coformulated with ATV (as Evotaz) or DRV (as Prezcoibix), or COBI as a component of Symtuza, in children aged <18 years. However, the Panel considers these fixed-dose combinations appropriate for pediatric use, given that the individual component drugs have been approved for use in children and adolescents who meet certain weight-based indications.

References

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